CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ETHALFLURALIN

Chemical Code # 002166, Tolerance # 00416
SB 950 # 292
July 23, 1987
Revised 10/5/89; 9/21/93

I. DATA GAP STATUS

Chronic, rat:	No data gap, no adverse effect
Chronic dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction rat:	No data gap, no adverse effect
Teratology rat:	No data gap, no adverse effect
Teratology rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect

Chromosome: No data gap, possible adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity: Not required at this time

----------**Note, Toxicology one-liners are attached**

* indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T930921
Revised by G. Chernoff, 10/05/89; Aldous, 9/21/93.

All relevant records listed by the Pesticide Registration Library as of 9/16/93 have been rectified with those listed in the Toxicology Summary. This includes studies up to Record No. 114148 (Document No. 416-036). There are also a few older records with record numbers over 900000.

These pages contain summaries only. Individual worksheets may contain additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED (ONCOGENICITY/CHRONIC)

RAT

**** 001 and 010 986160, 36354 and 36355** "A Two Year Dietary Evaluation of Ethalfluralin (Compound 94961) in the Fischer 344 Rat." (Lilly Research Labs, Report no. R-267 and R-277, 6-81) Ethalfluralin, 94.5%, Lot no. B30- Y64-35B, was fed in the diet to Fischer 344 rats, 30/sex/group for 2 years in **each of 2** replicate studies at levels of 0, 0.01, 0.025 or 0.075 % (4.2, 10.7 or 32.3 mg/kg/day, time-weighted average); NOEL = 0.01% of diet; NOEL for slight increase in liver weights is 0.025%; NOEL for benign mammary gland fibroadenomas is 0.01%. Initially reviewed as unacceptable. Later the study was classified as upgradeable if specified data could be supplied. With submission of the body weights, food consumption and tissue inventory, the study was upgraded to ACCEPTABLE. J. Remsen (Gee), 7-29-85, 1-10-86 and 7-23-87.

EPA 1-liner: Minimum. Oncogenic NOEL = 100 ppm (mammary gland fibroadenomas (F) - 35%.

018, 019 and 020 50467, 50468 and 50469 Individual body weights, food consumption and inventory of tissues given pathologic exam for 986160, 36354 and 36355.

CHRONIC

RAT

No study on file for separate rat chronic category; see "Combined, Rat" above.

DOG

**** 014 42703** "The Toxicity of Ethalfluralin (EL-161, compound 94961) Administered Orally to Beagle Dogs for One Year." (Lilly Research Labs, Report no. D01684, 11/85) Ethalfluralin, 95.5% was given orally by capsule to beagle dogs, 4/sex/group, at levels of 0, 4, 20 or 80 mg/kg/day; NOEL = 4 mg/kg; liver weight increase and siderosis at 80 mg/kg; hematology changes (consistent with hemolytic anemia) and thrombocytosis at 80 and 20 mg/kg. ACCEPTABLE. F. Martz, 7-13-86.

ONCOGENICITY

RAT

No study on file for separate rat oncogenicity category; see "Combined, Rat" above.

MOUSE

416-009 036353 "A two-year dietary evaluation of ethalfluralin (Compound 94961) in the B6C3F1 mouse", Lilly Research Laboratories, Greenfield, IN, July 1981. Report Nos. M-9167 and M-9177. Ethalfluralin, 94.5%, was fed to 60/sex for control and 40/sex/group at 100, 400 or 1500 ppm for 2 years in **each of 2 replicate studies. NOEL = 100 ppm (increased incidence of hepatocellular hyperplasia at high doses). Initially report was reviewed as unacceptable, based on lack of tissue inventory and need for clarification of statements on food consumption. These data were submitted in the rebuttal in 416-017 and as Record No. 50469 in 416-020, upgrading the study to **acceptable**. Originally, the study was flagged as indicating a "possible adverse effect", based on hepatocellular hyperplasia at 1500 ppm and to a much lesser extent at 400 ppm. Currently, studies are not normally flagged based on reversible changes at relatively high doses, therefore this study is no longer classified as indicating "possible adverse effects". J. Remsen (Gee), 7/29/85, 1/14/86, and 7/23/87; Aldous, 9/21/93.

EPA 1-liner: Minimum. Oncogenic NOEL > 1500 ppm (HDT); systemic NOEL <= 100 ppm (LDT) (increase in focal hepatocellular hyperplasia)

416-001 986159 Less complete version of 416-009 036353, above.

416-009 036352 One-year dietary study in mice (Study M-9157, April 1981), performed in B6C3F1 mice (15/sex/dose) at the same dose levels as the above oncogenicity study, Record No. 036353. Report was originally reviewed by J. Gee, and the CDFA Summary of Toxicology Data had placed both studies into one "1-liner". The 1-year study identified a few findings suggestive of liver response: slight increase in liver weights (1500 ppm, both sexes), and increases **in males only** of alkaline phosphatase (400 and 1500 ppm) and of SGPT (1500 ppm). There were no corresponding histopathological changes. A modest drop in RBC count in 1500 ppm females at 1 year may have been treatment-related. NOEL = 100 ppm. **No adverse effects**. "Acceptable" as an ancillary study (not designed as an independent chronic study). J. Remsen (Gee), 7/29/85, 1/14/86, and 7/23/87; Aldous, 9/21/93.

EPA 1-liner: Minimum. Oncogenic NOEL > 1500 ppm (HDT); systemic NOEL <= 100 ppm (LDT) (increase in focal hepatocellular hyperplasia)

REPRODUCTION

RAT

**416-002 986164 "Multi-Generation Reproductive Study with Ethalfluralin (Compound 94961) in the Fischer 344 Rat." (Lilly Research Labs, report no. R-58, R-73B, R-124B, 3/81) Ethalfluralin, 94.5%, was fed to groups of Fischer 344 rats, 25/sex/group, for a 3 generation, 1 litter/generation study, at levels of 0, 100, 250 or 750 ppm in diet (average of 0.0, 7.6, 18.8, and 56.8 mg/kg respectively). Reproductive NOEL = 750 ppm. Parental NOEL = 250 ppm (slight decrease in male body weights). High dose justification was given in rebuttal (Document No. 416-017). Previously reviewed as unacceptable due to a lack of histopathology on reproductive organs of F0 and F1 adults [J. Remsen (Gee)], 7-30-85, 1-16-86 and 7-22-87).

G. Chernoff reviewed supplemental information (Record #074926), and determined that the lack of histopathology made the study "not upgradeable" (9/26/89). Finally, an ancillary study was conducted to provide histopathology data (Record No. 114148). Essential information from that study filled the remaining data requirement (see below). Supplemented with those data, this study is now **acceptable**. Aldous, 9/20/93.

EPA 1-liner: Supplementary. Systemic NOEL = 250 ppm (slightly depressed body weight in males of all 3 generations); Reproductive NOEL = 750 ppm (HDT, no hydronephrosis in contrast to hydronephrosis reported in rat teratology study.)

416-013 036379 exact duplicate of 416-002 986164, above.

028 074926 Histopathology data supplemental to multi-generation study in record #986164.

416-036 114148 [ancillary study to 416-002:986164] Hoyt, J.A., Owen, N.V., and Adams, E.R., "A 7-Month Multigeneration Bridging Study of Ethalfluralin (EL-161, Compound 094961) Administered in the Diet to Fischer 344 Rats", Lilly Research Laboratories, Greenfield, IN, April 9, 1992. Ethalfluralin (Lot Number B30-Y64-35B, purity 95.66%). Fischer 344 rats were treated continuously for 10 weeks prior to mating, then on through lactation of F1 pups. One F1 pup/sex/litter was selected for treatment into adulthood. Treatments continued uninterrupted for selected F1 pups, for a typical post-weaning exposure of about 14 weeks before sacrifice. Essential data new to this ancillary study were histological examinations of F0 and F1 adults (negative for both generations). NOEL = 250 ppm for adults (increased liver weights). No reproductive effects were noted. Bright yellow urine and urine-stained fur were universal at 250 to 750 ppm, and two 100 ppm F1 females had some staining of fur in the urogenital area. Staining appears to be normal excretion products of this brightly colored compound. Study is **acceptable** as an ancillary study. **No adverse effects**. The study fills the final data gap for evaluation of reproductive effects. Kishiyama and Aldous, 9/20/93.

TERATOLOGY

RAT

002 and 012 986163 and 36377 "A Teratology Study with Ethalfluralin (Compound 94961) in the Wistar Rat." (Lilly Research Labs, Report no. R06880, 11/80) Ethalfluralin, 93.5%, was given by gavage in 10% acacia solution to 25 dams/group at levels of 0, 10, 75 or 250 mg/kg/day on days 6-15 of gestation; NOEL > 250 mg/kg; no adverse effects reported in dams or fetuses; UNACCEPTABLE, dose levels too low. J. Remsen (Gee), 7-29-85 and 1-16-86.

EPA 1-liner: Supplementary. Maternal NOEL > 250 mg/kg (HDT). Trend toward hydronephrosis in treated litters. Controls performed poorly (decreased live fetuses, increased resorptions, increased females resorbing, decreased fetal weight) therefore making comparisons questionable.

016 42828 (Lilly Research Labs, 7/81) Historical control data for Fischer 344 rats.

** 016 42829 "A Teratology Study of Orally Administered Ethalfluralin (EL-161) in the Rat." (Bioresearch Labs, Ltd., Report no. 82182, 11/11/85) Ethalfluralin, 95.5%, given by oral gavage to 25/group at levels of 0 (aqueous acacia), 50, 250 or 1000 mg/kg/day on days 6-15 of gestation; Maternal NOEL = 250 mg/kg (body weight); developmental NOEL > 1000 mg/kg/day (HDT); ACCEPTABLE. J. Parker, 7-30-86.

RABBIT

**012 36378 "A Teratology Study of Ethalfluralin (EL-161, compound 94961) Administered Orally to Dutch Belted Rabbits." (Lilly Research Labs, Report no. B01383, 1/83) Ethalfluralin, 94.0%, was given by gavage to groups of 20 rabbits at 0 (10% acacia solution), 25, 75, 150 or 300 mg/kg/day on days 6-18 of pregnancy; Maternal NOEL = 75 mg/kg (decreased weight gain, anorexia, increased abortions and liver weight); Developmental NOEL = 300 mg/kg. ACCEPTABLE. J. Remsen (Gee), 1-16-86.

EPA 1-liner: Minimum. Teratogenic NOEL = 75 mg/kg/day (sternal and cranial variants); fetotoxic NOEL = 75 mg/kg/day (increased resorptions); maternal toxic NOEL = 150 mg/kg/day (abortions).

002 31106 "Teratology Study (II) with Ethalfluralin (Compound 94961) in the Dutch-Belted Rabbit." (Lilly Research Labs, Report no. B-7160, 10-80) Ethalfluralin, 94.5%, given to groups of 9 to 12 rabbits by gavage on days 6-18 of gestation at doses of 0 (acacia solution), 75 or 250 mg/kg; maternal NOEL approximately 75 mg/kg; 4/6 fetuses with defects at 250 mg/kg/day in one litter - the effects included cleft palate, the females with fetuses with the defects reportedly had been markedly anorexic for a period of time; UNACCEPTABLE due to incidence of mortality and abortions with inadequate number of litters for evaluation. J. Remsen (Gee), 7-29-85.

EPA 1-liner: Supplementary. Appears positive for teratogenicity at 250 mg/kg dose. Inadequate litters to examine. Extreme stress from dosing procedure.

416-012 036373 Range-finding study preceding Record No. 31106, above. No DPR review is necessary, since definitive studies have been completed at higher dose levels. Aldous, 9/20/93.

416-001 986161 Exact duplicate of 012 036373, above.

416-002 036374 A second range-finding study preceding Record No. 31106, above. This study bracketed the range tolerated by dams. No DPR review is necessary, since definitive studies have been completed, and no grossly evident terata were found in this pilot study. Aldous, 9/20/93.

002 31105 "Teratology Study (I) with Ethalfluralin (Compound 94961) in the Dutch-Belted Rabbit." (Lilly Research Labs, report no. B-7079, 10-80) Ethalfluralin, 94.5%, was administered by gavage to groups of 15 pregnant rabbits on days 6-18 of gestation at dose levels of 0 (acacia solution), 250, 500 or 750 mg/kg/day; maternal NOEL < 250 mg/kg/day,

developmental toxicity NOEL ≥ 750 mg/kg/day. UNACCEPTABLE due to excessive abortions and lethality, only 14, 9, 6 and 2 per group were pregnant and survived to term. J. Remsen (Gee), 7-29-85.

EPA 1-liner: Supplementary. Teratogenic NOEL => 750 mg/kg (HDT).

SUMMARY: The initial reviews noted possible adverse reproductive or teratogenic effects but these occurred in the presence of maternal toxicity in Record Nos. 31105 and 31106. A subsequent study, Record No. 36378, did not report any cleft palates in any group even at a dose (300 mg/kg/day) higher than that at which an equivocal teratogenic effect was noted in 361106. The weight of evidence, therefore, is that ethalfluralin is not a developmental toxicant in the absence of maternal toxicity. J. Gee, 7-24-87.

GENE MUTATION

BACTERIA

** **011 36365** "The Effect of Ethalfluralin (Compound 94961) on the Induction of Reverse Mutations in S. typhimurium Using the Ames Test." (Lilly Research Lab, report no. 830307AMS1169, 5-83) Ethalfluralin, 95.5%, was tested in the plate incorporation assay with Σαλμονελλα τψπηιμυριυμ strains TA1535, TA1537, TA1538, TA98 and TA100 at five concentrations ranging from 0 to 1000 ug/plate. Tests were done in triplicate, with and without S9 from Aroclor induced rat liver, repeat trial. Weak mutagenic effect in TA100 and TA1535 with S9; TA100 also showed an effect with non-induced rat liver extract. J. Remsen (Gee), 1-13-86.

EPA 1-liner: Acceptable. Positive for increased revertents (base-pair mutations) in Σαλμονελλα strains tested: TA1537, TA1538, TA1535, TA98, TA100; positive in TA1535 - activated, TA100 (dose response) +/- activation.

011 36362 "The Effect of Ethalfluralin on the Induction of Bacterial Mutation Using a Modification of the Ames Test." (Lilly Research Labs, report no. 830404GPA1169, 6-83) Ethalfluralin, 95.5%, was tested by the gradient plate method with Σαλμονελλα τψπηιμυριυμ strains TA1535, TA100, TA1537, TA98, TA1538 and others. Concentrations tested were 0 to 1000 ug/ml in 4 ranges, with and without Aroclor induced and non-induced rat liver; A weak mutagenic effect was reported in TA100 with and without S9; TA1538 and TA98 without S9, range 100 to 1000 ug/ml. No repeat trial, single plate, inadequate protocol to describe method. UNACCEPTABLE. J. Remsen (Gee), 1-13-86.

EPA 1-liner: Acceptable. Positive for increased revertents in Σαλμονελλα and E. χολι. (TA1535, TA100, TA98) tested with and without metabolic activation.

002 986165 "Effect of Ethalfluralin (Lily Compound 94961) on the Induction of Bacterial Mutation using a Modification of the Ames Test." (Lilly Research Labs, report no. LBMS 1169, 11-80) Ethalfluralin, 96.4%, was tested in the gradient plate assay at concentrations from 0.1 to 1000 ug/ml. Σαλμονελλα τψπηιμυριυμ and E. χολι strains were tested. UNACCEPTABLE. Substantial modification of mutagenicity protocol with insufficient details for justification. No repeat experiment. No information on diffusion rate of test compound. J. Remsen (Gee), 7-29-95.

EPA 1-liner: Unacceptable. Non-mutagenic at concentration ranging from 1000-0.1 ug/ml +/- activation in Σαλμονελλα strains: G46, TA1535, TA100, C3076, D3052, TA1538, TA98 and E. χολι strains: WP2 and WP2 uvr A .

416-011 036357 Exact duplicate of 002 986165, above.

** 011 36371 "Forward Mutation in Σχηιζοσαχχηαρομψχεσ πομβε-P1 Test Substance: Ethalfluralin." (Life Science Research Roma Toxicology Centre, report no. 095005-M-03085, 5-85) Ethalfluralin, 95.5%, was tested with Σχηιζοσαχχηαρομψχεσ πομβε P1 at concentrations of 0, 12.5, 25, 50, 100, 200 or 300 ug/ml, 16 hours of exposure. No evidence of mutagenicity in the adenine operon is presented. ACCEPTABLE. J. Remsen (Gee), 1-13-86.

416-011 036369 Preliminary report of 011:036357, above.

416-011 036359 (Jan. 1983) Proposed protocols for future Ames tests.

MAMMALIAN CELLS

011 36366 "The Effect of Ethalfluralin (Compound 94961) on the Induction of Forward Mutation at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells." (Lilly Research Labs, report no. 830208MLA1169, 4/83). Cells exposed to ethalfluralin, 95.5%, for 4 hours at 0, 0.1, 0.25, 0.5, 0.75, 1.0, 2.5, 5.0 or 10.0 ug/ml with and without rat liver activation. UNACCEPTABLE: no repeat trial, no increase in mutation index reported. J. Remsen (Gee), 1-13-86.

EPA 1-liner: Acceptable. Negative for TK locus in L5178Y cells up to toxic doses.

SUMMARY: Ethalfluralin was weakly mutagenic in two bacterial species but no evidence was presented for an effect in the single trial in mammalian cells.

416-011 036372 Proposed protocols for mouse lymphoma point mutation assay (Jan. 1983).

CHROMOSOMAL EFFECTS:

in vitro

** **011 36370** "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells in vitro Test Substance: Ethalfluralin." (Life Science Research Roma Toxicology Centre, report no. 095003-M-02385, 6-18-85) Cells exposed to ethalfluralin, 95.5%, without rat liver activation for 24 hours at 0, 7.24, 22.9 or 72.4 ug/ml, with activation for 3 hours at 0, 5, 15.8, 50 or 85 ug/ml and harvested at 12 and 24 hours. Duplicate cultures, 100 cells scored/culture; increased aberrations at 24 hours with S9, 85 ug/ml. This effect is discussed in 017 050466 by G. Probst of Elanco as possibly attributable to causes other than ethalfluralin exposure. ACCEPTABLE. J. Remsen (Gee), 1-13-86 and 7-24-87.

416-011 036368 Preliminary report of 011:036370, above.

In vivo

011 36367 "The Effect of Ethalfluralin (Compound 94961) on the in vivo induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters." (Lilly Research Labs, Report No. 830214SCE1169, 3-83) Ethalfluralin, 95.5%, given single dose by gavage to 3 females per group at 0, 200, 300, 400 or 500 mg/kg, which were sacrificed after 21 hours. Score 25 metaphases in bone marrow/animal; no increase in SCE's, cycle delay noted at 400 and 500 mg/kg. UNACCEPTABLE. Tested only females without adequate justification, inadequate number of animals. J. Remsen (Gee), 1-13-86 and 7-23-87.

EPA 1-liner: Unacceptable. Negative for SCE induction (DNA repair test) in females (males not tested)

002 986166 "Dominant Lethal Study with Ethalfluralin (Compound 94961) in the Rat." (Lilly Research Labs, report no. R-159, 12-80) Ethalfluralin, 93.5%, administered by a single gavage dose at 0 or 5 gm/kg to 10 male Wistar rats/group. Mate with females, 1/wk for 10 wks. UNACCEPTABLE: (too few females per group). Study with TEM as positive control for this study is in 021, Record No. 50470. J. Remsen (Gee),7-30-85 and 7-23-87.

EPA 1-liner: Not acceptable. No evidence of dominant lethal effect.

416-011 036358 Exact duplicate of 002 986166, above

416-011 036360 Jan. 1983 protocol for an eventual SCE assay.

416-011 036361 Published SCE method (Neal and Probst) to use for an eventual SCE assay. (Same study was cited in 417-017:050465).

DNA DAMAGE/OTHER

BACTERIA

No study on file for this specific sub-category.

MAMMALIAN CELL CULTURES

** 002 986167 "Effect of Ethalfluralin (Compound 94961) on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat." (Lilly Research Labs, 6-80) Rat hepatocytes exposed to ethalfluralin, 96.4%, concentration levels of 0, 0.5, 1, 5, 10, 50, 100, 500 or 1000 nmoles/ml, 20 hours, scored 20 cells/concentration. Toxic at the two highest concentrations. Initially reviewed as unacceptable based on minimal protocol, number of cells scored. Upgraded in rereview with the rebuttal in 017. The guidelines do not specify that more than one rat needs to be used. Because of the number of concentrations scored, the small number of cells scored for each becomes a less serious deficiency and the study is upgraded to ACCEPTABLE status. J. Remsen (Gee), 7-29-85 and 7-23-87.

EPA 1-liner: Acceptable. Negative for UDS, cytotoxic at 500 and 1000 moles/ml.

NEUROTOXICITY

Not required at this time.